Eur J Cancer Clin Oncol, Vol. 19, No. 1, pp. 5–10, 1983.
Printed in Great Britain.

0277-5379/83/010005-06$03.00/0

Androgen Excretion in Women with a Family History of Breast Cancer or with Epithelial Hyperplasia or Cancer of the Breast*

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Abstract—*Urinary testosterone and androstanediol were measured by gas chromatography in four groups of premenopausal subjects: 22 healthy women (control group), 21 healthy women with a family history of breast cancer (familiality group), 39 patients with breast lumps which consisted of ductal or lobular hyperplasia (hyperplasia group) and 18 patients with infiltrating breast carcinoma (carcinoma group). On the basis of normal values found in our laboratory, steroid levels were above normal in 4.5% of the controls, 4.7% of the familiality group, 38.5% of the hyperplasia group ($P < 0.01$ vs controls) and 61.1% of the carcinoma group ($P < 0.001$ vs control group). The mean testosterone level in the carcinoma group (11.3 ± 6.78 S.D.) and the mean androstanediol level in the hyperplasia group (47.25 ± 31.0 S.D.) were significantly higher than those of the control group (testosterone 6.25 ± 3.48 S.D., androstanediol 32.55 ± 20.0 S.D.). No significant difference was found in mean testosterone or androstanediol levels between the control group and the familiality group (testerone 5.41 ± 3.6 S.D., androstanediol 29.38 ± 15.89 S.D.). We conclude that increased excretion of androgenic steroids is a hormonal abnormality common to breast cancer patients and to patients with breast epithelial hyperplasia, but not to subjects with a family history of carcinoma of the breast.*

INTRODUCTION

FAMILY history of breast cancer [1] and fibrocystic disease of the breast with hyperplasia of ductal or lobular epithelium [2] has been reported as a factor of risk for breast cancer. In a previous paper, Grattarola [3] showed that in patients with mammary fibrocystic disease the excretion of urinary testosterone and androstanediol was significantly higher than normal, and urinary testosterone excretion was also raised in some breast cancer patients [4].

The aim of the present study was to confirm that the excretion of androgenic steroids is significantly higher than normal in a statistically significant number of patients with breast cancer or patients at enhanced risk because of the presence of areas of ductal or lobular hyperplasia in the breast, and to observe if the same hormonal abnormality is present in women at risk because of a family history of breast cancer.

Accepted August 1982.
*This study was supported in part by grant No. 81.01387.96 from the Consiglio Nazionale delle Ricerche, Rome.

MATERIALS AND METHODS

Since January 1980 a study on urinary excretion of testosterone and androstanediol has been carried out on four groups of subjects. The control group consisted of 22 women (age 31–49 yr, mean 39.1 ± 5.26 S.D.) satisfying the following conditions: no family history of breast cancer; no present or previous mammary pathology; no other benign or malignant neoplasias; and no endocrine, metabolic or chronic disease. The familiality group consisted of 21 women (age 31–48 yr, mean 40.2 ± 5.01 S.D.) with a family history of breast cancer in the mother, sister or other relatives. The hyperplasia group consisted of 39 patients (age 27–48 yr, mean 39.08 ± 6.06 S.D.) subjected to biopsies of breast lumps which were histologically diagnosed as hyperplasia of

ductal or lobular epithelium. The carcinoma group consisted of 18 patients (age 33–52 yr, mean 43.46 ± 5.62 S.D.) subjected to biopsies of breast lumps which were histologically diagnosed as infiltrating carcinoma.

All these subjects from the Outpatient Department of the Istituto Nazionale Tumori of Milan were included in the study consecutively, and the study was closed after admission of the hundredth subject. All of them were still menstruating and none had taken any hormonal drug for at least 3 months before hormonal examination. No subject had been given a long-term course of cortisone or was taking digitalic or antihypertension drugs, tranquilizers or somnifacients for chronic diseases.

The steroids were measured in a sample of a 24-hr urine specimen collected between the 18th and 22nd days of the menstrual cycle. Urinary testosterone (17β-hydroxyandrosta-4-en-3-one) and androstanediol (5α-androstane-3α,17β-diol) were measured by gas chromatography using the method of Mauvais-Jarvis *et al.* [5], as previously reported [3]. Urine from the 18 breast cancer patients was collected before mastectomy, and urine from the patients in the hyperplasia group was assayed within 6 months after biopsy. The hormonal study was done blind, i.e. for each patient the evaluation of steroid excretion was done without knowing in which of the four groups the patient was. On the basis of normal values checked in our laboratory [3], steroid excretion was considered higher than normal when testosterone excretion values were higher than 13.0 μg/24 hr or androstanediol higher than 60.0 μg/24 hr.

Statistical comparisons between the excretion values of androgens in the four groups of subjects were made by use of Student's *t* test after the data were converted to a logarithmic scale. $P<0.05$ was considered significant. The chi-square test was used to compare the number of patients with steroid excretion higher than normal in each of the four groups.

RESULTS

Control group

No patient in this group exceeded the upper limit of 13.0 μg/24 hr for testosterone (range 0.0–13.0 μg/24 hr), and the mean excretory value was 6.25 ± 3.48 μg/24 hr (Fig. 1). The mean excretory value for androstanediol was 32.55 ± 20.0 μg/24 hr (range 0.0–80.0 μg/24 hr) (Fig. 2), and 1 patient exceeded the value of 60.0 μg/24 hr. In this group steroid excretion higher than normal was detected in 1 of 22 patients (4.5%) (Table 1).

Familiality group

The excretion values for testosterone (mean 5.4 ± 3.6 S.D. μg/24 hr; range 0.0–11.8 μg/24 hr) (Fig. 1) and androstanediol (mean 29.38 ±15.89 S.D. μg/24 hr; range 1.0–61.0 μg/24 hr) (Fig. 2) did not significantly differ from those of the control group (Table 2). Only 1 of 21 (4.7%) patients showed steroid excretion higher than normal (Table 1).

Hyperplasia group

The mean excretory value for testosterone (6.97 ± 4.44 μg/24 hr; range 1.5–21.5 μg/24 hr) (Fig. 1) did not significantly differ from that of the control group (Table 2), but the mean excretion value for androstanediol (47.25 ± 31.0 μg/24 hr; range 9.4–130.0 μg/24 hr) (Fig. 2) was significantly higher ($P<0.05$) than that of the control group (Table 2). Fifteen of 39 patients (38.5%) showed steroid excretion values higher than normal (4 patients of testosterone, 9 of androstanediol and 2 of both androgens). In this group the number of patients with steroid excretion above the normal range was significantly higher than in the control group ($\chi^2=6.7$; $P<0.01$) (Table 1).

Carcinoma group

The mean excretory value for testosterone (11.3 ± 6.78 μg/24 hr; range 3.2–31.0 μg/24 hr) (Fig. 1) was significantly higher than that of the control group ($P<0.01$) and the hyperplasia group ($P<0.01$) (Table 2). The mean excretory value for androstanediol (44.96 ± 33.9 μg/24 hr; range 6.9–108.6 μg/24 hr) (Fig. 2), while greater than that of the control group, was not statistically significant (Table 2). Eleven of 18 patients (61.1%) showed steroid excretion higher than normal (4 of testosterone, 5 of androstanediol and 2 of both androgens). The number of abnormal patients in this group was significantly greater than in the control group ($\chi^2=12.5$; $P<0.01$) (Table 1).

DISCUSSION

This study demonstrates that many patients with ductal or lobular mammary hyperplasia, a known risk factor for breast carcinoma, have a hormonal abnormality in common with many breast cancer patients, namely supranormal urinary excretion of either testosterone, androstanediol or both. It therefore seems reasonable to hypothesize that the hormonal abnormality detected in hyperplasia patients may be at least partly responsible for their increased risk of developing cancer and that its correction may decrease the risk. In contrast, patients with familial risk for breast cancer do not show

supranormal urinary androgen excretion, suggesting that their risk may be mediated by mechanisms different from those of hyperplasia patients.

Our data confirm previous reports of increased urinary excretion of androgen metabolites in patients with fibrocystic disease [3] or cancer of the breast [4], and support Grattarola's hypothesis that androgens may play a role in the development of breast disease [3, 4, 6–8].

The high incidence of increased urinary excretion of testosterone and androstanediol in breast cancer patients before mastectomy, as shown in this study, is very close to the previously reported [6, 9] incidence in metastasized breast cancer patients. Patients with metastatic breast cancer and increased urinary excretion of testosterone and androstanediol have been shown to have hormone-dependent tumors because of the high percentage of remission of metastases after ovariectomy [6, 9]. It is therefore possible that increased urinary excretion of testosterone and androstanediol is also indicative of hormone-dependent tumors in patients with operable breast cancer.

In a series of publications, subnormal excretion values of urinary 11-deoxy-17-ketosteroids have been reported in primary operable [10] and metastasized breast cancer patients [11–13], in patients with benign breast disease [14] and in women before the clinical onset of breast cancer [15]. On this basis, it is generally believed that low values of 11-deoxy-17-ketosteroids are associated with increased risk of breast cancer or with a worse prognosis after the development of metastases. These findings apparently contrast with our data and with previous reports from our laboratory of urinary testosterone excretion values higher than normal in women with fibrocystic disease of the breast or with early or advanced breast cancer. So far our studies on urinary testosterone have not been repeated by others, and only a few reports of blood testosterone levels in breast cancer patients are available. The results are very conflicting: no significant difference has been found between breast cancer patients and controls by some

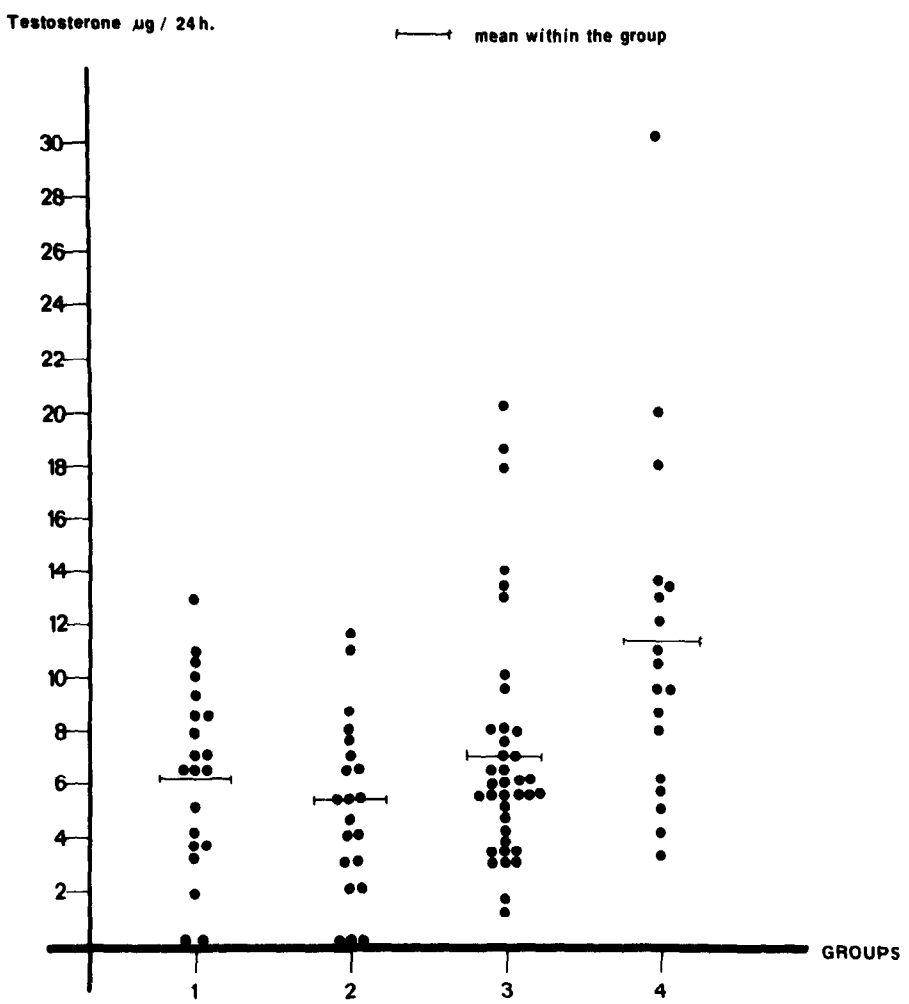

Fig. 1. Individual testosterone excretion values in the four groups studied: 1, control group; 2, familiality group; 3, hyperplasia group; 4, carcinoma group.

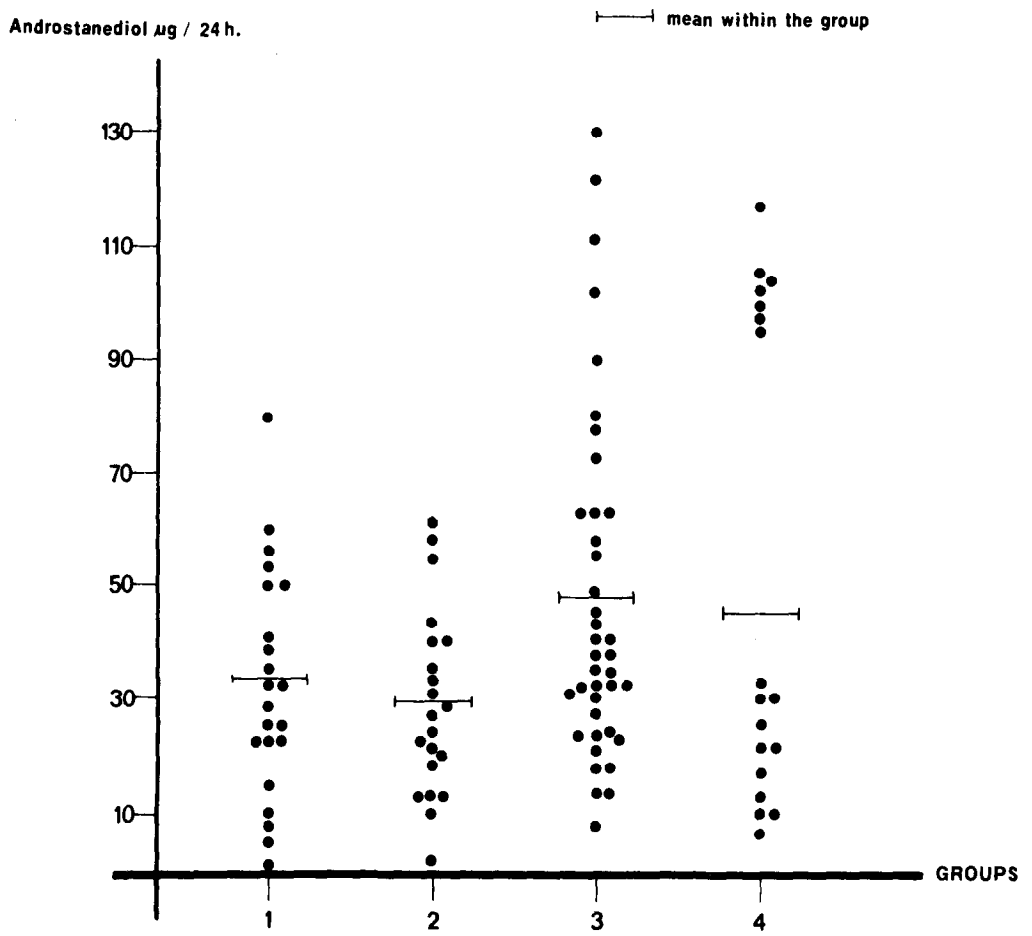

Fig. 2. Individual androstanediol excretion values in the four groups studied: 1, control group; 2, familiality group; 3, hyperplasia group; 4, carcinoma group.

Table 1. Number of patients with testosterone excretion values higher than 13.0 µg/24 hr or androstanediol higher than 60.0 µg/24 hr

Group	No. of cases	Elevated androgenic excretion No. of cases	%	Significance*
Control	22	1	4.5	
Familiality	21	1	4.7	NS
Hyperplasia	39	15	38.5	$P < 0.01$
Carcinoma	18	11	61.1	$P < 0.001$

*NS, not significant. Statistical significance vs control group.

Table 2. Mean excretion values of testosterone and androstanediol in the four groups

Group	No. of cases	Testosterone (µg/24 hr)	Androstanediol (µg/24 hr)
Control	22	6.25 ± 3.48*	32.55 ± 20.00
Familiality	21	5.41 ± 3.60	29.38 ± 15.89
Hyperplasia	39	6.97 ± 4.44	47.25 ± 31.00‡
Carcinoma	18	11.30 ± 6.78†	44.96 ± 33.90

*Mean ± S.D.
†$P < 0.01$, carcinoma group vs the other groups.
‡$P < 0.05$, hyperplasia group vs control group.

authors [16–18], whereas significantly increased testosterone levels in breast cancer patients have been reported by others [19, 20]. Malarkey *et al.* [21] found increased testosterone levels in premenopausal but not in postmenopausal breast cancer patients. Most of these papers have been accurately reviewed by Zumoff [22] and criticized for poor selection of patients or inadequate methodology.

The data from the literature of subnormal urinary 17-ketosteroid excretion in breast cancer patients and our findings of increased urinary testosterone and androstanediol are not entirely comparable: urinary 11-deoxy-17-ketosteroids mainly reflect adrenal androgen production [23], whereas testoterone is largely secreted by the ovaries [24] and androstanediol is mainly derived by conversion of dihydrotestosterone in the target tissues [25, 26]. Furthermore, Wang *et al.* [27] have suggested the possibility that subnormal androgen production may be a genetic marker of predisposition to breast cancer. No difference in testosterone or androstanediol excretion values between normal controls and women with a family history of breast cancer was found in our study. These findings further support the hypothesis that two different groups of androgenic substances have been detected in the studies previously reported and in ours.

In conclusion, our present data show increased excretion values of some androgens (testosterone and androstanediol) found only occasionally in healthy premenopausal women and in those with a family history of breast cancer, but rather frequently (38.5%) in women with ductal or lobular breast hyperplasia and predominantly (61.1%) in those with operable breast cancer. On the basis of these results, we suggest the use of urinary measurement of testosterone and androstanediol in women with hyperplastic alterations of the breast epithelium as a method of evaluating the oncogenic risk in these cases, which might lead to preventive therapy.

Acknowledgement—The authors thank Ms. B. Johnston for editing and preparing the manuscript.

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